

planning. After 3 months a complete response was observed in 46%, and 7% had partial response.

**Conclusions:** Using the HYPERcollar, deep hyperthermia treatment of HNC was found to be safe, feasible, with good compliance and promising outcome. These promising early clinical results culminated in the use of hyperthermia as a standard addition to reirradiation. We will now embark on a study for (chemo-)irradiation combined with hyperthermia in primary head and neck cancer.

---

#### Debate: Particle therapy: Randomised trials are obligatory

---

##### SP-0336

**For the motion: particle therapy: randomised trials are obligatory**

D. De Ruyscher<sup>1</sup>

<sup>1</sup>University Hospital Gasthuisberg, Radiation Oncology, Leuven, Belgium

Randomized controlled trials (RCTs) are the gold standard for comparative effectiveness research of medical interventions. Treatment guidelines rank evidence of using a hierarchy with evidence from RCTs at the highest level, Level I. Many authorities require Level I evidence from RCTs for registration and reimbursement of a new drug. When Level I evidence is not available, the treatment is often viewed as being “unproven”. Ideally, every new diagnostic or interventional procedure should be tested in RCTs before becoming standard care to avoid ineffective or harmful treatments. The reason is that even treatments supported by a clear biological rationale and strong pre-clinical data may not produce a therapeutic gain; examples include the detrimental effect of erythropoietin when used together with radiotherapy for head and neck cancer or class 1c antiarrhythmic agents in myocardial infarction patients. The unexpected result of these studies provides a strong argument in favour of randomization.

Engineers and physicists often tackle the problem of obtaining “evidence” by making models to calculate the quantitative relationship between parameters and a particular outcome. The acceptance of the latter kind of empirical model spring from its ability to predict the outcome of experiments with accuracy, reliability and prospective reproducibility that is sufficient to be useful. The analogy with human biology is far from perfect because of the complexity of the processes involved. In physics controlling a rather limited set of known experimental conditions will suffice to standardize outcome measurements. The utility of models predicting clinically relevant outcomes could theoretically indeed be established by prospective comparisons between expected and observed outcomes. However, this is no simple task and has not been accomplished convincingly in the past. Nearly all proton therapy studies are retrospective, with heterogeneous patient groups recruited over long time periods, treated with varying techniques and with often very incomplete follow-up data. The radiobiology of the complex DNA damage in the Bragg peak is large unexplored and is not taken into account in current proton TPS. Some TCP and NTCP models are without doubt of merit for photon therapy, but they should not be extrapolated blindly to proton therapy as long as the latter models too have undergone extensive validation. The model-based approach is clearly a field where much more research is needed before this can be accepted as an alternative for RCTs. Except for some quite extreme cases, e.g. in some CNS and childhood tumours, randomised trials

are still necessary, scientifically, legally and for obtaining reimbursement.

##### SP-0337

**Against the motion**

H. Langendijk<sup>1</sup>

<sup>1</sup>UMC Groningen, Radiation Oncology, Groningen, The Netherlands

---

#### Joint Symposium with Proffered Papers: ESTRO-PROS: Paediatrics: Late effects

---

##### SP-0338

**Neuro-cognitive sequelae after brain irradiation**

R.D. Kortmann<sup>1</sup>

<sup>1</sup>University of Leipzig, Radiation Therapy, Leipzig, Germany

**Purpose / Objective:** Cognitive impairment is frequently present in childhood brain tumour survivors and greatly impacts psychosocial development and quality of survival. Major contributing factors are related to tumour, the presence of hydrocephalus, surgery, chemotherapy and radiotherapy. The neurocognitive functions primarily involved are including memory, attention, visual perceptual ability and verbal function.

**Materials and Methods:** The majority of data are essentially based on past treatments with varying treatment volumes (craniospinal irradiation followed by a boost, whole brain irradiation, local irradiation with varying dose prescriptions) for medulloblastoma, low grade glioma, ependymoma, germ cell tumours and leukemia. The literature is replete of data based on retrospective evaluations spanning many years during which general disease management was improved. Additionally, radiotherapeutic approaches considerably changed with the introduction of 3 D conformal technologies including IMRT and recently proton therapy that essentially permit a more precise coverage of tumour while sparing normal brain tissue.

**Results:** Post radiation changes include a wide spectrum of abnormalities from subclinical changes detectable only by MRI to focal neurological deficits and intellectual impairment. It appears that all changes are likely to result from complex alterations within several functional compartments with the following contributing factors: damage to vessel structures, deletion of oligodendrocyte progenitor cells and mature oligodendrocytes (white matter), deletion of neural stem cell population in the hippocampus. Additionally, the tumours significantly differ between the inherent disabling potential with respect to tumour location and the therapeutic approach. The major risk factors are young age at treatment and a dose relationship in whole brain irradiation. Recent data indicate that particular radiosensitive regions of the brain are more susceptible to the adverse effects of radiation such as frontal lobes, temporal lobe and hippocampus including anatomical subcompartments in which neurogenesis occurs (subventricular zone). However, the relationship between radiation dose to these areas and a decline in neurocognitive function remains a controversial issue. Recent data indicate that radiation dose to neuronal progenitor cell niches and temporal lobes causes a decline in cognitive function. Modern radiotherapy technologies are able to selectively reduce the dose to organs at risk. Correspondingly, reducing the dose to the hippocampus in adults appears to preserve memory with conformal avoidance of the hippocampal neural stem cell compartment during whole-brain radiotherapy (recently